Remarks

Claims 1-47 are pending in the application. Claims 1 and 34-47 have been canceled with the present Amendment. Claims 3, 7, 9, and 32 are amended as above. Claims 8, 11-17, 21-25, and 27-29 are withdrawn from further consideration as being drawn to nonelected species. New claims 48-68 have been added. Support for new claims 48 can be found on page 16, lines 18, through page 18, line 7, of the Specification as originally filed. Support for claim 49 can be found on page 18, lines 8-12. Support for claim 50 can be found on page 8, line 19. Support for claim 51 can be found on page 8, lines 19-22. Support for claim 52 can be found on page 8, lines 20. Support for claim 53 can be found in original claim 53. Support for claim 54 can be found on page 17, line 1. Support for claim 55 can be found in original claims 2 and 3. Support for claim 56 can be found on page 12, lines 3-6. Support for claim 57 can be found on page 17, lines 9-13. Support for claim 58 can be found on page 18, line 14, through page 19, line 2. Support for claim 59 can be found on page 19, lines 12-17. Support for claim 60 can be found on page 19, lines 15-17. Support for claim 61 can be found on page 19, lines 12-18. Support for claim 62 can be found on page 19, lines 17-18. Support for claim 63 can be found on page 21, lines 13-22. Support for claim 64 can be found on page 21, lines 13-22. Support for claim 65 can be found on page 21, lines 16-17. Support for claim 66 can be found on page 21, lines 21-22, page 22, lines 6-9, and page 29, line 1. Support for claim 67 can be found on page 22, lines 11-13. Support for claim 68 can be found on page 13, lines 8-10. Applicant submits that no new matter has been added by these amendments. Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

I. Rejections under 35 U.S.C. § 112, first paragraph, for lack of written description.

Claims 2-7, 9-10, 18-20, 26, and 30-33 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner maintains that the Specification does not sufficiently teach the claimed method of identifying a test compound that affects a biological event of interest wherein the biological event of interest is being detected using any type of inducible reporter gene that produces a product that is secreted

by the cell and is detectable. The Examiner seems to believe that one of skill in this art could not envision the method using any type of inducible reporter gene except nitric oxide synthase. This is incorrect. As the Examiner has pointed out in the Office Action, the Specification mentions other reporter genes besides nitric oxide synthase. For example, the Specification on page 17, lines 8-10, lists luciferase, β-lactamase, secreted alkaline phosphatase, and green fluorescent protein as other possible reporter genes useful in the claimed method. Therefore, one of skill in this art reading the Specification would understand the inventive method to include the use of reporter genes besides nitric oxide synthase.

In addition to those reporter genes listed in the Specification, any other inducible reporter gene that produces a gene product that is secreted by the cell and detectable could be used in the claimed method. The Applicant's exmplification using nitric oxide synthase should not be used to unduly limit the Applicant's patent rights. What the Applicant invented was a method that is useful in high throughput screening of test compound to identify compounds with the ability to interfere with a particular biological event. This general method could be practiced using a variety of reporter genes and reporter gene products. One of skill in this art would understand this from reading the Specification, therefore, the Applicant has satisfied the written description requirement and requests that the rejection be withdrawn.

The Examiner has also rejected claims 2-3 and 5 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the specification does not sufficiently teach the claimed method of identifying a test compound that affects a biological event of interest wherein any type of molecular sensor is used to detect the reporter gene product. Again, the Examiner wishes to limit the claims based on the example using a nitric oxide sensor. As would be appreciated by one of skill in the art, the molecular sensor used in the claimed invention will depend on the reporter gene product being assayed for. There are many different molecular sensors known, and one of skill in the art would understand that any of these molecular sensors could be used in the claimed invention. The Applicant should not be limited to nitric oxide sensors.

Claims 2-3 and 32 have also been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the

specification does not teach the claimed method wherein fluorescence-activated bead sorting is used in the identifying step because the bead has no fluorescence feature. Claim 32 has been amended to depend from claims 5, 6, 7, 8, and 9, which recite a molecular sensor associated with the solid support. In certain embodiments of the invention, the molecular sensor has a "fluorescence feature" that can be used to sort the solid supports using fluorescence-activated bead sorting. Applicant submits that amended claim 32 obviates the Examiner's rejection and requests that the rejection be removed.

Claims 2-3 and 33 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner believes that the specification does not teach the claimed method of identifying a test compound that affects a biological event of interest wherein the step of identifying the compounds is a combination of detecting the production of the reporter gene product and decoding the tags on the solid support. Applicant respectfully submits that this is incorrect. This aspect of the invention is described in the application on page 3, line 23, through page 4, line 2; on page 20, lines 9, through page 21, line 10; and in Example 1 on page 25, line 21, through page 26, line 1. In addition, on page 26, line 1, the Applicant cites and incorporates by reference Nestler *et al. J. Org. Chem.* 59:4723, 1994, as describing how tags are used in the field of combinatorial chemistry to encode the synthetic history or structural features of a compound attached to a solid support. Applicant submits that one of ordinary skill in this art reading the application would understand that the step of identifying as recited in claim 33 involves the combination of detecting the production of the reporter gene product and decoding of the tag on the solid support. The claimed invention should not be limited to the combination of detecting NO production and decoding the tag as the Examiner has suggested because the decoding of a tag could be used with the detection of any reporter gene product, not just NO. Applicant, therefore, requests that the rejection be removed.

II. Rejections under 35 U.S.C. § 112, second paragraph, as being indefinite.

Claims 2-7, 9-10, 18-20, 26, and 30-33 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner states that the contacting step of claim 2 and the claimed structural feature of the test compounds of claim 3 are incomplete and indefinite because it is unclear how the compounds are contacted with the cell when they are attached to the solid support. Applicant have amended claim 3 so that it is clear that the test compounds are provided attached to the solid support but are then subsequently cleaved from the solid support to allow the compound to contact the cell. Applicant requests that the amended claim is definite and requests that the rejection be removed.

The combination of claims 2, 3, and 32 have been rejected under 35 U.S.C. § 112, second paragraph, as being incomplete and indefinite because there is no fluorescence feature on the solid support. Applicant respectfully submits that the amendment to claim 32 obviates this rejection. The molecular sensor attached to the solid support has the fluorescence feature being detected by fluorescence-activated bead sorting and once the bead is detected the test compound that was attached to the support can be identified by decoding the tags attached to the support. Applicant requests that the rejection be withdrawn

The combination of claims 2, 3, and 33 have also been rejected under 35 U.S.C. § 112, second paragraph, as being incomplete and indefinite because there is no fluorescence feature on the solid support and the identifying step of claim 33 contradict the identifying step of claim 2. Applicant submits that the combination of claims is not indefinite. The Examiner has stated that the claims are indefinite because there is no fluorescence feature on the solid support. But the solid support does not have to have a fluorescence feature. Claim 33, unlike claim 32, does not recite the use of fluorescence-activated bead sorting; therefore, a fluorescence feature is not needed. In fact, the beads may be selected for decoding of the tags attached may be selected based on any criteria such as a color change, location on a plate, *etc.* A fluorescence feature is not needed to carry out the invention described in claim 33 as it depends from claims 2 and 3.

The Examiner also believes the identifying step of claim 33 contradicts the identifying step of claim 2. This is an incorrect reading of the combination of claims 2 and 33. Claim 2 describes the identification of a test compound. Claim 33 recites the decoding of a tag on a solid support from which the test compound was cleaved. By decoding the tag, one practicing the invention can learn the identity of the test compound. Therefore, claim 33 complements claim 2

by describing a particular way of identifying the test compound. The combination of claims 2, 3, and 33 are definite and complete, and Applicant requests that the rejection be removed.

Claim 9 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that "molecular sensor" does not have an antecedent basis in claim 4. Applicant has amended claim 9 to depend from claim 6 rather than claim 4, thereby obviating the Examiner's rejection. Applicant requests that the rejection be removed.

III. Rejections under 35 U.S.C. § 102.

Claims 2, 10, 18-20, 26, and 30-31 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Foulkes *et al.*, U.S. Patent 5,580,722. Foulkes *et al.* teach a method of determining whether a chemical not previously known to be modulator of protein biosynthesis is capable of specifically transcriptionally modulating the expression of a gene encoding a protein of interest. Foulkes *et al.* also mention that nitric oxide synthase might be a protein of interest. The Examiner believes that based on these teachings Foulkes *et al.* anticipates the presently claimed invention. This is incorrect.

The presently claimed invention includes identifying a test compound based on the production of a reporter gene product that is secreted by the cell, detectable, and indicative of the occurrence or non-occurrence of a biological event. Foulkes *et al.* does not describe the detection of a reporter gene product that is secreted by the cell. Rather Foulkes *et al.* describes the detection of a measurable signal, particularly mRNA and protein levels. No signals other than mRNA levels and protein levels are described as being detected in the method of Foulkes *et al.* Foulkes *et al.*, therefore, in no way describes the detection of a secreted gene product as in the claimed invention. Therefore, Foulkes *et al.* cannot anticipate the claimed invention, and the Applicant requests that the rejection be removed.

Claims 2-4, 10, 18, and 26 have been rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Borchardt *et al. Chemistry & Biology* 4(12):961-68, 1997. The Examiner states that Borchardt *et al.* teach a method of detecting small molecule-protein interactions within yeast cells. The Examiner maintains that the concluding remarks of Borchardt *et al.* stating that "it should be possible to use many other types of visual readouts, such as changes in cell

morphology, secretion of reporter enzymes or translocation of fluorescent proteins" render the claimed invention unpatentable for lack of novelty. This is incorrect. In order for a disclosure to anticipate the claimed invention, it must be an enabling disclosure. Borchardt *et al.* do not provide an enabling disclosure. The comment regarding the secretion of reporter enzymes is included in the concluding remarks of their paper describing other possibilities for the nanodroplet assay. These are mere future possibilities and are not enabled disclosures that could anticipate the claimed invention. For example, Borchardt *et al.* do not mention any possible secreted reporter enzymes that might be useful. Borchardt *et al.* cannot anticipate the claimed invention because Borchardt *et al.* does not enable one of skill in the art to practice the claimed invention. Instead, the work of the Applicant actually put the public in possession of the claimed invention. Application requests that the rejection be removed.

Claims 2-4, 10, 18, and 33 have been rejected by the Examiner under 35 U.S.C. § 102(b) as being anticipated by Still *et al.*, U.S. 5,565,324. Still *et al.* teach methods and compositions for encoding combinatorial libraries. The Examiner maintains that the screening method of Still *et al.* comprises (1) providing a plurality of beads carrying the final product compounds, (2) providing cells wherein binding a surface membrane protein produces an observable product, (3) the final product is detached from the bead in order to react with the cells, and (4) identifying the final product compounds that cause the expression of the observable product. Even if Still *et al.* teaches such a method, they do not teach a reporter gene product that is secreted by the cell as claimed in the present application. Since Still *et al.* do not teach this aspect of the claimed invention, they cannot anticipate the claimed invention, and Applicant requests that the rejection be removed.

IV. Rejections under 35 U.S.C. § 103.

Claims 2-4, 10, 18, 26, and 33 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Still *et al.*, U.S. Patent 5,565,324, and Ashby *et al.*, U.S. Patent 5,569,588. The Examiner describes the teaching of Still *et al.* as above but indicates that Still *et al.* do "not expressly include using yeast cell[s] in the method of screening compounds." The Examiner cites Ashby *et al.* as teaching methods and compositions for modeling the transcriptional

responsiveness of an organism, including yeast, to a candidate drug. The Examiner maintains that it would have been obvious to include yeast cells in a cell-based assay for screening compounds for a characteristic of interest such as physiological or biological activity as taught by Ashby *et al.* in the method of Still *et al.* However, even if these references teach what the Examiner claims they do, the references still fail to teach that the reporter gene product is secreted by the cell. The secretion of the reporter gene product in the claimed invention allows for the easy detection of the product, for example, at the bead from which the test compound was cleaved. Ashby *et al.* and Still *et al.* do not teach that the reporter gene product is secreted from the cell; therefore, even in combination, they fail to render obvious the claimed invention. Applicant respectfully requests that the rejection be removed.

Claims 2-7, 9-10, 18-20, 30-31, and 33 stand rejected under 35 U.S.C. § 103(a), as being unpatentable over Still *et al.*, U.S. Patent 5,565,342, and Misko *et al.*, *Analytical Biochemistry* 214(1):11-16, 1993. The Examiner states that Still *et al.* do not expressly include using a nitric oxide molecular sensor for detecting NO synthase activity in a cell-based assay and the nitric oxide molecular sensor is 2,3-aminonaphthalene (DAN). Although Misko *et al.* teaches the monitoring of NO synthase activity using 2,3-diaminonaphthalene (DNA) in a 96-well plate format, the combined references do not teach the use of NO synthase as an inducible reporter gene, the expression of which results in a secreted gene product, NO. In Misko *et al.*, the assay method is taught for the purpose of further understanding the role of NO synthase not as a reporter gene to be used in understanding other biological events. Still *et al.* also do not teach the use of NO synthase as a reporter gene and certainly do not teach the detection of a reporter gene product secreted by the cell as explained above. The Examiner states that it would have been obvious to a person of ordinary skill in the art to include the use of a nitric oxide molecular sensor for detecting NO synthase activity in a cell-based assay wherein the NO molecular sensor is DAN. Applicant respectfully disagrees. Still *et al.* teaches detection of a reporter gene product but it is not secreted from the cell as in the claimed invention. Therefore, one of ordinary skill in the art would not have been motivated to combine the teaching of Still *et al.* with the teaching of Misko *et al.* because the reporter gene product, NO, is secreted from the cell in order to detect the presence of the NO using a nitric oxide molecular sensor. Since there is no

teaching, suggestion, or motivation to combine these two references, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness.

In addition, even if there were a teaching or suggestion to combine the references, the combined references would still not teach all aspects of the claimed invention. Specifically, the combined references do not teach that the reporter "gene product is secreted by the cell". Also, the combination of Still *et al.* and Misko *et al.* does not indicate that an assay based on NO detection could be successfully used in screening a plurality of test compounds. Uncertainties regarding diffusion of the NO molecule, levels of NO necessary for accurate detection, and the overall successful incorporation of this biological system into a screening method show that the Examiner has not provided evidence that there is a reasonable expectation of success even if there was a teaching to combine the references.

Since there is no teaching or suggestion to combine the references, no teaching of all the aspects of the claimed invention, and no reasonable expectation of success in combining the references, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness. Applicant request that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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